REMARKS

This reply is filed in response to the Office Action dated October 22, 2009 ("Office Action"). Upon entry of the present amendment, claims 1 and 4-20 will be pending, claims 2 and 3 having been canceled without prejudice. Applicants have amended claim 1 to incorporate the limitation of claim 2 and added new claims 16-20. Support for the new claims can be found throughout the specification, for example, at page 5, lines 14-35; and page 6, lines 3-4. See in particular the definition of "cryoprecipitation increase suppression rate" and the formula by which it can be calculated provided at page 5, lines 23-30. No new matter has been introduced.

Interview Summary

Applicants thank Examiner Kam for the telephone interview on January 13, 2010, with Applicants' representative, Dr. Jeannie Wu (Reg. No. 56,265), which was requested to discuss the objection to claim 2 and confirm that the objected-to claims would be allowable if amended to incorporate all of the limitations of the claims from which they depend. Instead, Examiner Kam indicated that claim 2 should have been included in the obviousness rejection. Applicants requested a new Office Action to replace the current one, so that this new rejection of claim 2 could be properly set forth. Examiner Kam denied the request and suggested that Applicants address the outstanding obviousness rejection of claims 1, 4, 6, 8-12 and 14 as though it also included a rejection of claim 2. It was not clear to Applicants' representative whether Examiner Kam considered objected-to claims 5, 7, 13 and 15 otherwise allowable, or believes they should have been included in the obviousness rejection.

Withdrawn Claim Rejections

Applicants note with appreciation that the Examiner has withdrawn the rejections under 35 U.S.C. § 112, first and second paragraphs.

Objections to claims

The Examiner objected to claims 2, 5, 7, 13 and 15 as allegedly depending from a rejected claim. Applicants have amended claim 1 to incorporate the limitations of claim 2 and submit that amended claim 1 is allowable for at least the reasons set forth below. Claims 5, 7, 13 and 15 depend from claim 1 and are allowable for at least the same reasons. Claim 2 has been canceled. Applicants respectfully request that this objection be reconsidered and withdrawn.

35 U.S.C. § 103

The Examiner rejected claims 1, 4, 6, 8-12 and 14 as allegedly obvious over Smith et al. (U.S. Patent No. 5,792,838; "Smith"). For the purpose of moving this application toward allowance, Applicants have amended claim 1 to incorporate the limitations of claim 2. As noted above, although claim 2 was not included in this rejection, the Examiner indicated during the telephone interview that it should have been included. Since the present Office Action does not state any reasons for rejecting claim 2 as obvious, Applicants are not certain how to address the Examiner's unstated concerns with respect to this claim.

As an initial matter, Applicants note that the relevant disclosure of Smith appears to be similar to that of Flink (WO 99/37329), which was cited in the Office Action dated March 12, 2008 ("March 12 Action") to support the obviousness rejection raised therein. As Applicants explained in the reply to the March 12 Action filed September 11, 2008 ("September 11 Reply"), all of the examples in Flink involve an IgG antibody at a concentration of 1 mg/ml. In the September 11 Reply (at pages 7-8), Applicants presented a number of reasons and supporting evidence for why the amended claims presented in that reply would not have been obvious over Flink. For example, Applicants demonstrated that the art understood there are substantial differences between IgG and IgM antibodies with respect to their storage, stability, and precipitation properties. See the discussion of the Phillips et al. and the Page and Thorpe articles discussed in detail in the September 11 Reply at pages 7-8. Applicants established that these known differences between IgG properties and IgM antibody properties would not have led one skilled in the art to predict that conditions suitable for storage of IgG antibodies would also be

suitable for IgM antibodies. Further, Applicants explained that the results described in the instant specification showing that IgM can be successfully stored in citric acid buffer at low temperatures (i.e., below 7°C) were unexpected, given the known propensity of IgM antibodies to cryoprecipitate at such temperatures. Thus, the present application solves a previously recognized and unsolved need. The Examiner apparently found these reasons to be persuasive, since the obviousness rejection over Flink was withdrawn in the subsequent Office Action dated December 19, 2008.

As the Examiner acknowledged in the present Office Action at page 3, Smith does not disclose any actual experiments using an IgM antibody. All of the actual examples described in Smith involve IgG (e.g., the commercially available antibody CAMPATH 1H). Smith demonstrated that, in the presence of copper ion, IgG antibody molecules are susceptible to degradation, particularly at high temperature (e.g., 37°C or higher; see, e.g., Example 1). Smith quantified the degree of degradation by size exclusion HPLC analysis, taking the extent of formation of "Peak C" (an IgG degradation product) as a measure of the extent to which the IgG antibody had been degraded. (See Smith at col. 5, lines 1-5.) Smith did not report having measured any sort of aggregation or precipitation of her antibody molecules, so one of ordinary skill reading Smith would have no idea whether the various chelators tested by Smith would have any effect at all on aggregation or precipitation of the tested IgG. The disclosures of Smith have nothing to do with solving the problem of precipitation (or cryoprecipitation) of antibodies in general or IgM in particular, and certainly raise no expectation that cryoprecipitation of IgM can be suppressed by use of a particular sort of buffer. Phillips et al. taught that in 2001 (i.e, 3 years after the date Smith issued as a patent) aggregation of IgM during storage was still considered to be a significant problem: "[The] purified [IgM] Ab was still prone to aggregate and precipitate on storage. Extra work would be necessary...to find a suitable stabilizing formulation for the pure [IgM] Ab" (page 238, right column). Clearly, Smith did not solve this cryoprecipitation problem.

Applicants also point out that Smith did not disclose experiments utilizing concentrations of antibody that even approach the "at least 20 mg/ml" concentration required by the claims.

None of the IgG solutions[1] studied by Smith exceeded an antibody concentration of 11.3 mg/ml, and the only two examples (Examples 8 and 9) in Smith that employed a citrate buffer (as required by the present claims) used 2 mg/ml or less of the IgG antibody. The Office Action at page 3, line 5, alleges that Smith discloses a solution containing 20 mg/ml of an antibody. Smith does say that the formulations "preferably contain 0.5 to 20 mg/ml of the antibody," **but this is explicitly in the context of the CAMPATH-1H IgG antibody, not antibodies in general and certainly not IgM in particular**. (See, col 4, lines 51-54, where the first half of the sentence that mentions 0.5 to 20 mg/ml makes it clear that this refers to "the case of the humanised antibody CAMPATH-1H.") It cannot be said to have been "obvious" to produce a solution containing IgM at a concentration of 20 mg/ml or greater merely because Smith said one particular IgG, CAMPATH-1H, is preferably formulated at a concentration of 0.5 to 20 mg/ml, especially given the known propensity of IgM to aggregate at high concentrations. (It would be even less obvious to produce a solution containing IgM at a concentration of 25 mg/ml or greater, as specified in new claim 17.) Nor would it have been "obvious" from anything disclosed in Smith to maintain an IgM solution (particularly a highly concentrated IgM solution) at 1° to 7°C, where the art taught that IgM would cryoprecipitate at such a temperature.

In view of the foregoing, Applicants submit that the present claims are not obvious over Smith. The Office Action does not suggest any reason why one would have expected that a solution containing citrate and at least 20 mg/ml IgM could have been maintained at the temperature specified in claim 1 without extensive cryoprecipitation. Since neither the motivation nor the expectation of success necessary for a *prima facie* case of obviousness of what was claim 2 (and is now claim 1) can be found in the art, the rejection fails on that ground. Further, Applicants have provided evidence of surprising results to support the nonobviousness of the claims: contrary to all expectations, cryoprecipitation of IgM can be greatly reduced in the method of the invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 are respectfully requested. If the Examiner decides to maintain the obviousness rejection despite the present amendment of claim 1 to include the limitations of claim 2 (which was not rejected

[1] As mentioned above, Smith used IgG, not IgM as presently claimed, in her experiments.

for obviousness in the present Office Action), Applicants note that the next Office action cannot be made final.

CONCLUSION

Applicants respectfully request that all claims be allowed. Applicants do not concede any positions of the Examiner that are not expressly conceded above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims. Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14875-0158US1.

Respectfully submitted,

Date: January 21, 2010

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